REMARKS

Reconsideration is requested.

Claims 36-38 and 44-45, have been canceled, without prejudice. Claim 49 has been added based on the disclosure, for example, of Example 2, page 22, line 11. Claim 32 has been amended to specifically indicate in the preamble that the cells are expressing cancer-testis antigens, as indicated in step (d) as previously recited. No new matter has been added, the amendments are not believed to raise new issues requiring further search and/or consideration. Upon entry of the above amendments, claims 32-35, 39-43 and 46-49 will be pending. The amendments have been made to advance prosecution by obviating the remaining rejections. At a minimum, the amendments place the application in better form for appeal by materially reducing the issues for appeal.

Specifically, claim 32 has been amended and claim 38 has been canceled, without prejudice, to obviate the Section 112, second paragraph, rejection of claims 32-47. The applicants believe the prior recitation of CTA presenting cells was clear to one or ordinary skill in the art however claim 32 has been amended to recite equivalent cells and to indicate correspondence between the preamble and final step. Entry of the above will obviate the Section 112, second paragraph, rejection of claims 32-48, thus reducing the issues for appeal. Entry of the above and withdrawal of the Section 112, second paragraph, rejection of claims 32-48 are requested.

The Section 112, first paragraph, rejection of claims 32-48 is obviated by the above and the following as well as the attached evidence.

The evidence presented in the Amendment of July 23, 2002 was incorrect and potentially misleading. The applicant regrets any inconvenience caused by the presentation of the earlier submitted evidence. Specifically, the tables included with the Amendment of July 23, 2002 were appreciated to be in error only after review of the same with the Office Action of October 22, 2002. The applicant believes the Tables submitted with the Amendment of July 23, 2002 were the result of a word processing error and should be disregarded. The Examiner is requested to consider the attached and the following as a further elaboration of the evidence provided in the present specification

The claims have been amended, without prejudice, to specify that peripheral blood mononuclear cells are collected, activated, etc. Support for the same may be found, for example, at page 14, line 9 to page 15, line 13 of the specification as well as Example 1, page 19, lines 17-19; Example 2, page 22, lines 9-13; Example 3, page 25, line 4-7; Example 4, page 28, lines 5-7; Example 5, page 30, lines 14-16; and Example 6, page 33, lines 12-15, of the specification. The Examiner has examined similar subject matter (see, claims 39-43 and page 3, lines 6-7 of the Office Action dated October 22, 2002 (Paper No. 8)) such that the amendments are not believed to raise new issues requiring further search and/or consideration. Entry of the amendments is requested.

The Examiner has recognized at page 3, lines 6-7 of Paper No. 8 that

> "The specification discloses a method for generating APC cells expressing TAA belong[ing] to [the] cancer-testis antigen (CTA) family by treating cells derived from PBMC of cancer patents with advanced stage of disease or healthy individual... (see examples 1-6)." (Emphasis added.)

The claims have been amended to recite those aspects of the disclosed invention which the Examiner appears to have recognized is described and enabled by the specification, to advance prosecution.[1]

The Examiner appears to appreciate that each of the Examples of the specification involved the use/collection of peripheral blood mononuclear cells (PBMCs) from cancer patients or healthy subjects. See, page 19, lines 18-19 (Example 1), page 22, lines 10-11 (Example 2), page 25, lines 6-7 (Example 3), page 28, lines 6-7 (Example 4), page 30, lines 15-16 (Example 5) and page 33, lines 14-15 (Example 6).

Independent reporting of the results from cancer patients and healthy subjects was/is not believed to be required as the applicants believed, and continue to believe, that one of ordinary skill will appreciate from the teaching of the application that either source of PBMCs will be useful in practicing the disclosed invention.

The Examiner's citation of various art in support of an alleged recognition of unpredictability in the art is necessarily relying on art which has not benefited from a review of the present application. Reliance on the cited art in this regard is therefore necessarily of limited value. Moreover, the Examiner's concern regarding mechanisms of action is, with due respect, submitted to be of little relevance to the ability of one of ordinary skill in the art to make and use the claimed invention as an applicant is not (and should not be) required to explain or disclose how or why the claimed invention operates.

---

[1] The Examiner's apparent contradiction of the above quoted passage in lines 12-13 of page 3 of Paper No. 8 is not understood and clarification is requested in the event the rejection is maintained.

The applicants have exemplified the presently claimed invention, as apparently recognized by the Examiner, and withdrawal of the Section 112, first paragraph, rejection of claims 32-48 is requested.

For completeness and in response to the Examiner's request on page 5 of Paper No. 8, the applicants submit the following comments.

The expanded data presented in the Amendment of July 23, 2002 was, as noted above, in error. The error was not appreciated until after receipt of the Office Action dated October 22, 2002. The applicant regrets any confusion which may have been caused by the applicants statement that the tables "were extracted from the present application" (see, page 5 of Amendment).

The attached tables present the data from the specification, expanded to separate results from cells obtained from cancer patients and healthy subjects. Specifically, the specification contains six tables one each for the six Examples. See, pages 22 (Example 1), 24 (Example 2), 27 (Example 3), 30 (Example 4), 32 (Example 5), and 35 (Example 6) of the specification.

In the attached tables, the original data for each example have been expanded by providing the number of healthy and cancer affected subjects.

In the attached there are six tables, each one corresponding to the six examples of the application.

Each Table in Examples 1-6 of the specification has three columns and a number of rows.

The first column in the tables of the specification, starting from the left, starts with the hypomethylating agent used in the example, then lists the CTAs tested in that

example. The second column in the Tables of the specification [i.e., (-)] identifies testing the presence of the CTAs in cells not treated with the hypomethylating agent. The third column in the Tables of the specification [i.e., (+)] identifies testing the presence of the CTA in cells treated with the hypomethylating agent. The couple of numbers in the second and third columns of the Tables of the Specification are read as the number of expressed CTAs of the number of tested subjects.

It shall be noted that the same experimental protocol is repeated for each of the six Examples as far as the RT-PCR analysis of CTA and primers utilized to assess CTA expression (see, for example, page 21, line 16).

One of ordinary skill in the art reading the Specification will appreciate that blood samples were taken from cancer patients in advanced stage of disease or healthy subjects (page 19, lines 18-19). Blood samples were taken both from cancer patients in advanced stage of disease and healthy subjects. See, for example, page 13, lines 17-20, where the general enablement of the invention is disclosed (*the cells are collected from a subject, in particular a mammal, more in particular a human*). The next sentence describes a specific embodiment within the general teaching (*in a possible embodiment of the present invention, said human is a cancer patient*). The ordinarily skilled reader will understand that, since the vaccine comprising the APCs of the present invention may be, in a preferred embodiment of the invention, autologous (see page 18, lines 8-10), it is apparent that the cells [PBMC] will be taken from a cancer patient and the APC thereby obtained will be given to the same patient. On the other hand, in another preferred embodiment of the present invention, the vaccines are allogeneic (ibid., lines

11-16). This means that the cells may be used both as APCs and in the form of "reservoir" of pooled cancer antigens (in order to manufacture vaccines).

The ordinarily skilled person will further understand from the present specification that PBMC can be withdrawn both from cancer patients and healthy subject as PBMCs from these two sources are indistinguishable in view of their capacity to be transformed in APCs.

After withdrawal of blood from cancer patients and healthy subjects in the Examples, PBMC were purified (page 19, lines 17-19). PBMC were then activated (page 19, line 20 to page 20, line 2), then the samples were split in two groups: one group was treated with the hypomethylating agent (5-AZA-CdR) and the other group was not treated with 5-AZA-CdR (page 20, lines 12-14). Therefore, 5-AZA-CdR treated cells are in the right column of the Tables of the specification under the (+) sign and non treated cells are in the center column under the (-) sign.

The attached tables are divided in two groups: cancer patients and healthy subjects.

Reviewing Example 1 of the specification and the attached tables, the Examiner is urged to appreciate that there are three cancer patients and one healthy subject, which corresponds to four subjects in Example 1 in the description (page 22). In the case of MAGE-1, and the table for cancer patients in the attached, the split sample of activated cells not treated with 5-AZA-CdR shows that none of the three samples tested for CTA resulted in positive MAGE-1, and in the table for healthy subjects, the split sample of activated cells not treated with 5-AZA-CdR also shows that the single sample did not test for CTA. The total of samples tested without being treated with 5-AZA-CdR

therefore in the Table on page 22 of the specification, in the second column (i.e., "-") is "0/4" or zero positives of four tested. Similarly, for the samples treated with 5-AZA-CdR in Example 1 of the attached tables, four of four (i.e., "4/4") samples (three cancer patients and one healthy subject) tested positive for MAGI-1.

Similar results are demonstrated for the remaining Examples.

The specification presented the data gathered without distinction between healthy and cancer patients because it was the genuine intention to demonstrate that PBMC work well whether they originate from healthy subjects or cancer patients. The specification is believed to demonstrate the irrelevance of the origin of the cells, as claimed.

The applicant respectfully submits that the specification, and attached demonstrates that PBMC express CTAs when treated with the method herein disclosed.

The applicants submit that the specification is enabling for the pending claims. Withdrawal of the Section 112, first paragraph, rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
B. J. Sadoff
Reg. No. 36,663

BJS:plb/pc
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

EXAMPLE 1

CANCER PATIENTS : n = 3

	Not treated with 5-AZA-CdR		Treated with 5-AZA-CdR	
	Tested	Positive	Tested	Positive
MAGE-1	3	0	3	3
MAGE-2	NT	NT	NT	NT
MAGE-3	3	0	3	3
MAGE-4	NT	NT	NT	NT
NY-ESO-1	3	0	3	3
GAGE 1-6	3	0	3	3
SSX-2	3	1	3	3

HEALTHY SUBJECTS: n = 1

	Not treated with 5-AZA-CdR		Treated with 5-AZA-CdR	
	Tested	Positive	Tested	Positive
MAGE-1	1	0	1	1
MAGE-2	NT	NT	NT	NT
MAGE-3	1	0	1	1
MAGE-4	NT	NT	NT	NT
NY-ESO-1	1	0	1	1
GAGE 1-6	1	0	1	1
SSX-2	1	1	1	1

EXAMPLE 2

CANCER PATIENTS : n = 2

	Not treated with 5-AZA-CdR		Treated with 5-AZA-CdR	
	Tested	Positive	Tested	Positive
MAGE-1	2	0	2	2
MAGE-2	2	0	2	2
MAGE-3	2	0	2	2
MAGE-4	2	0	2	2
NY-ESO-1	2	0	2	2
GAGE 1-6	2	0	2	2
SSX-2	2	1	2	2

HEALTHY SUBJECTS: n = 2

	Not treated with 5-AZA-CdR		Treated with 5-AZA-CdR	
	Tested	Positive	Tested	Positive
MAGE-1	2	0	2	2
MAGE-2	2	0	2	2
MAGE-3	2	0	2	2
MAGE-4	2	0	2	2
NY-ESO-1	2	0	2	2
GAGE 1-6	2	0	2	2
SSX-2	2	0	2	2

EXAMPLE 3

CANCER PATIENTS: n = 4

	Not treated with 5-AZA-CdR		Treated with 5-AZA-CdR	
	Tested	Positive	Tested	Positive
MAGE-1	4	0	4	4
MAGE-2	4	0	4	4
MAGE-3	4	0	4	4
MAGE-4	4	0	4	4
NY-ESO-1	4	0	4	4
GAGE 1-6	4	0	4	4
SSX-2	4	0	4	3

HEALTHY SUBJECTS: n = 10

	Not treated with 5-AZA-CdR		Treated with 5-AZA-CdR	
	Tested	Positive	Tested	Positive
MAGE-1	6	0	6	6
MAGE-2	6	0	6	5
MAGE-3	7	0	7	6
MAGE-4	7	0	7	7
NY-ESO-1	10	0	10	10
GAGE 1-6	10	0	10	10
SSX-2	10	0	10	10

EXAMPLE 4

CANCER PATIENTS: n = 2

	Not treated with 5-AZA-CdR		Treated with 5-AZA-CdR	
	Tested	Positive	Tested	Positive
MAGE-1	2	0	2	2
MAGE-2	2	0	2	1
MAGE-3	2	0	2	2
MAGE-4	2	0	2	2
NY-ESO-1	2	0	2	2
GAGE 1-6	2	0	2	2
SSX-2	2	0	2	2

HEALTHY SUBJECTS: n = 2

	Not treated with 5-AZA-CdR		Treated with 5-AZA-CdR	
	Tested	Positive	Tested	Positive
MAGE-1	2	0	2	2
MAGE-2	2	0	2	2
MAGE-3	2	0	2	2
MAGE-4	2	1	2	1
NY-ESO-1	2	0	2	2
GAGE 1-6	2	0	2	1
SSX-2	2	0	2	1

EXAMPLE 5

CANCER PATIENTS: n = 3

	Not treated with 5-AZA-CdR		Treated with 5-AZA-CdR	
	Tested	Positive	Tested	Positive
MAGE-1	3	0	3	3
MAGE-2	2	0	2	2
MAGE-3	3	0	3	3
MAGE-4	3	0	3	3
NY-ESO-1	3	0	3	3
GAGE 1-6	2	0	2	2
SSX-2	3	0	3	3

HEALTHY SUBJECTS: n = 9

	Not treated with 5-AZA-CdR		Treated with 5-AZA-CdR	
	Tested	Positive	Tested	Positive
MAGE-1	9	0	9	9
MAGE-2	1	0	1	1
MAGE-3	9	0	9	9

MAGE-4	1	0	1	1
NY-ESO-1	3	0	3	3
GAGE 1-6	2	0	2	2
SSX-2	3	0	3	3

EXAMPLE 6

CANCER PATIENTS: n = 3

	Not treated with 5-AZA-CdR		Treated with 5-AZA-CdR	
	Tested	Positive	Tested	Positive
MAGE-1	3	0	3	3
MAGE-2	3	0	3	3
MAGE-3	3	0	3	3
MAGE-4	3	0	3	3
NY-ESO-1	3	0	3	3
GAGE 1-6	3	0	3	3
SSX-2	3	0	3	3

HEALTHY SUBJECTS: n = 4

	Not treated with 5-AZA-CdR		Treated with 5-AZA-CdR	
	Tested	Positive	Tested	Positive
MAGE-1	4	0	4	4
MAGE-2	4	0	4	4
MAGE-3	4	0	4	4
MAGE-4	4	0	4	4
NY-ESO-1	4	0	4	4
GAGE 1-6	4	0	4	4
SSX-2	4	0	4	4